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Formation of Diethyl 2-Amino-1-cyclopentenylphosphonates: A Simple Synthesis with a Unique Mechanism

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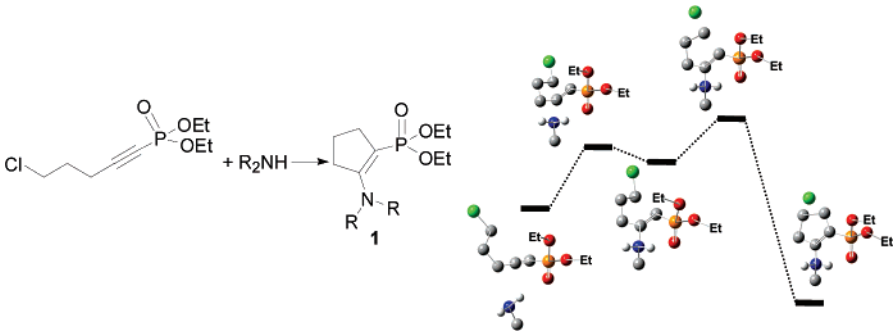

Reaction of diethyl 5-chloro-1-pentynylphosphonate with primary and secondary amines produces novel 2-amino-1-cyclopentenylphosphonates, **1**, in excellent isolated yields (79−88%). Calculations supported by experimental facts point to a two-step mechanism: an initial amine addition to give a zwitterionic intermediate followed by cyclization and proton transfer. Calculations rule out the formation of an enamine as an intermediate.

Introduction

2-Amino-1-alkenylphosphonates are useful intermediates in organic synthesis for the preparation of other phosphorus-containing compounds.[1] Particularly active in these areas is the Palacios group, which uses them to prepare various phosphorylated nitrogen heterocycles[2] and the pharmacologically important β-aminophosphonates.[3] (*E*)-2-Diethylaminophosphonate was prepared in 1963 by Saunders and Simpson through addition of diethylamine to ethynylphosphonate.[4] In 1964 it was reported that propynylphosphonate adds secondary amines to form 2-dialkylamino-1-propenylphosphonates but in poor yields (10−15%) and contaminated with 2,2-bis(dialkylamino)propanylphosphonate.[5] Chatta and Aguiar reported in 1973 that the addition of R_2NH to 1-alkynylphosphonates proceeded in high yields to produce mixtures of (*Z* and *E*)-2-aminoalkenylphosphonates, the latter stereoisomer presumably due to the high temperatures employed (refluxing acetonitrile) and to the use of a large excess of amine.[6] Acheson et al. in 1986 found that R_2NH added to ethynylphosphonate to form mixtures of *E* and *Z* products.[7] Ionin reported that addition of secondary amines to 1-alkynylphosphonates in the presence of Cu(I) salts in polar solvents at 120 °C gave improved yields and exclusive (*E*) selectivity.[8] Beletskaya used an Arbuzov reaction of the corresponding

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(1) Some recent references are: (a) Palacios, F.; de Retana, A. M. O.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767−8774. (b) Palacios, F.; de Retana, A. M. O.; Pascual, S.; de Munain, R. L.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61*, 1087−1094.

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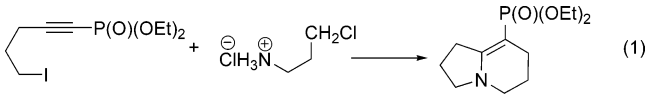
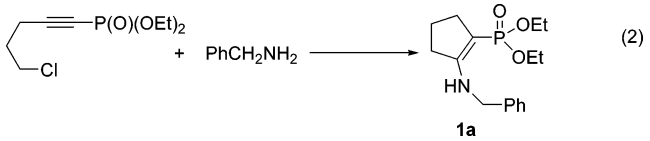
bromo enamine (at 80−110 °C) to obtain 2-aminoalkenylphosphonates with retention of stereochemistry.[9] Palacios has prepared 2-amino-1-alkenylphosphonates by the addition of primary amines to allenylphosphonates in refluxing acetonitrile.[10] He has also prepared them by lithiation of phosphonates followed by reaction with nitriles.[11] They have also been prepared by reaction of chloroimines with lithiated methylphosphonate; however, mixtures of 2-iminophosphonates and 2-aminoalkenylphosphonates were obtained.[12] Our interest in 2-amino-1-alkenylphosphonates stems from our previous investigations into the preparation of 3-amino-1-alkenylphosphonates with group IV reagents.[13] We were particularly interested in the recent publication by Ma and co-workers on the synthesis of indolizidines and quinolizidines by cyclization involving 5-iodo-1-alkynylphosphonate in refluxing acetonitrile (eq 1).[14]



(1)

Results and Discussion

We decided to reinvestigate the Ma reaction with 5-chloro-1-pentynylphosphonate and a simpler amine (in its free form). Thus, 5-chloro-1-pentynylphosphonate was allowed to react with benzylamine at 25 °C. On aqueous workup, diethyl 2-benzylamino-1-cyclopentenylphosphonate, **1a**, was obtained (eq 2).



(2)

1a

The present one-pot reaction proceeds very smoothly in the absence of catalysts and inorganic additives. The cyclization is very general for primary and secondary amines and tolerates hydroxy groups (**1g**, **1h**) as shown in Table 1. Also, 2-amino-1-cyclopentenylphosphonates, **1**, are essentially a novel class of compounds[15] and are stable to water and silica gel chromatography. The addition products with secondary amines, such as pyrrolidine and piperidine, while also undergoing facile additions to give β-enaminocyclopentenylphosphonates, ^{31}P δ ~30 ppm, are more prone to hydrolysis under acidic conditions but are nevertheless stable in neutral aqueous solution and on silica.

Structures **1** were confirmed by GC/MS, ^{31}P, ^{13}C, and ^{1}H NMR, and elemental analysis. The doublet of triplets in the ^{1}H NMR spectrum of compounds **1** in the region ~2.8 ppm corresponds to the allylic hydrogens on C5 split by phosphorus. Also, the triplet in the region ~3.4 ppm is indicative of allylic hydrogens on C3 which are shifted downfield due to the proximity of the nitrogen atom. In addition, the doublet in the region ~164 ppm in the ^{13}C NMR spectrum corresponds to C2 split by phosphorus; the other quaternary C1 was not observed.

TABLE 1. Compounds 1 Obtained From 5-Chloro-1-pentynylphosphonate and Amine

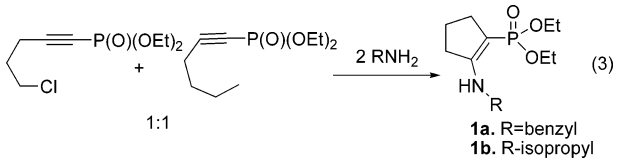
1	amine	isolated yield,[a] % (conversion)[b]
a	benzylamine	88 (>98)
b	isopropylamine	85 (>98)
c	*n*-propylamine	87 (>98)
d	amylamine	83 (>98)
e	cyclohexylamine	79 (>98)
f	methylamine[c]	85 (>98)
g	2-amino-1-propanol	88 (>98)
h	ethanolamine	87 (>98)
i	2-methoxyethylamine	87 (>98)
j	pyrrolidine	87 (>98)
k	piperidine	87 (>98)

[a] After silica gel chromatography. [b] Estimated by GC/MS and ^{31}P NMR. [c] Methylamine 40% in water.

Mechanistic Considerations. To choose the most probable mechanism, experimental facts have to be considered. The difference in the course of the reaction between 5-iodo- and 5-chloro-1-alkynylphosphonates is striking. In the former case it was suggested that the reaction with amine occurs initially on the C−I bond followed by deprotonation and addition to the triple bond (eq 1).[14] In our case we clearly have a different mechanism. The first step must be different and therefore involve amine addition to the C−C triple bond followed by cyclization. This must result from the different reactivity of the C−I and C−Cl bonds vis-à-vis the C−C triple bond.

The reaction discussed here provides only 2-amino-1-cyclopentenylphosphonates under different conditions (neat and in some cases in solution). In addition, all reactions under neat conditions proceeded at comparable orders and were all complete within 5 h. These results are different from previous observations of Lhommet et al., who found that methyl 7-chloro-2-heptynoate cyclizes exclusively to the cyclohexenylcarboxylate with primary amines under neat conditions but observed that mixtures of the corresponding azaheterocycle and cyclohexenylcarboxylate were obtained in the presence of different solvents with and without NaI.[16] Thus, while Lhommet's reported reaction mechanism involving formation of an enamine supports his results in different solvents (and is probably different under neat conditions), we tend to believe that the current reaction (eq 2) shares a common mechanism for all the different reaction conditions.

To gain more insight into the mechanism and examine the possibility of formation of an enamine intermediate, we performed a competitive reaction of 1:1 mixtures of 1-hexynylphosphonate and 5-chloro-1-pentynylphosphonate, respectively (either neat, in THF, or MeOH), with 2 equiv of benzylamine or isopropylamine. These experiments resulted exclusively in the formation of the 2-amino-1-cyclopentenylphosphonates **1a** or **1b**, respectively (eq 3, Table 1).



(3)

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(13) Some recent references: (a) Quntar, A. A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379. (b) Quntar, A. A.; Srebnik, M. *J. Org. Chem.* **2006**, *71*, 730−733. (c) Quntar, A. A.; Srebnik, M. *J. Organomet. Chem.* **2005**, *690*, 2504−2514. (d) Dembitsky, V. M.; Quntar, A. A.; Haj-Yehia, A.; Srebnik, M. *Mini-Rev. Org. Chem.* **2005**, *2*, 343−357.

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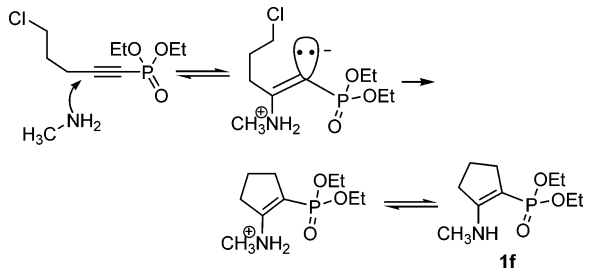
SCHEME 1. Possible Mechanism of Formation of 1f



In addition we found a rate acceleration of about 1 order of magnitude in favor of **1** formed from 5-chloro-1-pentynylphosphonate and benzylamine or ethanolamine (estimated $t_{1/2}$ of approximately 1 h at 25 °C) compared with enamine formation from 1-hexynylphosphonate and the same primary amines (estimated $t_{1/2}$ of about 10 h at 25 °C).

Since an inductive effect of the chloride over four bonds is an unlikely explanation for the selectivity observed in the competitive experiments, we believe that the mechanism does not involve formation of an enamine. Calculations performed addressed this mechanistic question (see the Experimental Section for details). The calculations considered the **1f** compound obtained from diethyl 5-chloro-1-pentynylphosphonate and methylamine as a model. Following our assumption that the same mechanism takes place in different environments (neat, MeOH, THF, etc.), it is reasonable to assume that the surrounding molecules participate only through solvation effect and do not have a chemical role in the reaction mechanism.[17] Therefore, the suggested mechanism, see Scheme 1, involves no participation of external molecules. It is a stepwise mechanism where the first step involves an initial addition of the amine to the triple bond to give a zwitterionic intermediate, while the next steps involve cyclization followed by proton loss leading to the 2-amino-1-cyclopentenylphosphonates.

The zwitterionic intermediate could proceed through a *Z* transition state where the amine group is cis to the phosphonate group (as depicted in Scheme 1 and **TS-a1** in Figure 1a). Conversely, the amine group can be situated trans to the phosphonate leading to an *E* transition state (**TS-b1** in Figure 1b). Parts a and b of Figure 1 summarize the relative energies of both the *Z* and *E* TSs and intermediates along the first step of the reaction profile, respectively. Additional results at various calculation levels are given as the Supporting Information.

The results show that in the first step, which involves amine addition, the respective barriers of the two paths differ. The higher barrier is obtained for path b, which results in the *E* zwitterion. The *Z* intermediate, where the amine is situated trans to the lone pair of the anion, **int-a1**, gains additional stabilization compared to the *E* intermediate, **int-b1**, due to both hyperconjugation effects of carbanions[18] as well as the existence of a hydrogen bond between the amine and the phosphonate. Hence, the higher barrier obtained for path b is clear.

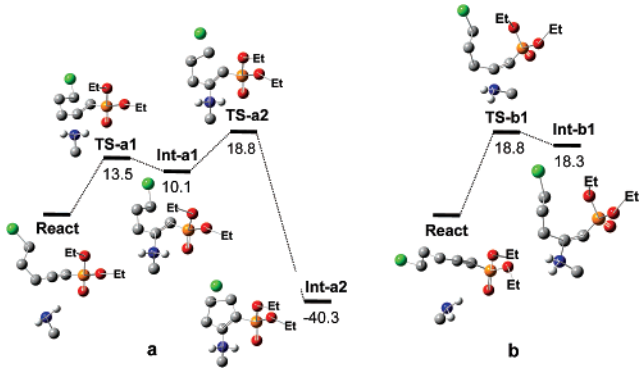


FIGURE 1. Calculated energy profile of (a) methyl amine *Z*-addition to diethyl 5-chloro-1-pentynylphosphonate followed by cyclization and (b) methyl amine *E*-addition to diethyl 5-chloro-1-pentynylphosphonate. Energies (in kcal/mol) are obtained at the B3LYP/6-31G* level of calculation with PCM. Only the nitrogen's hydrogens are depicted.

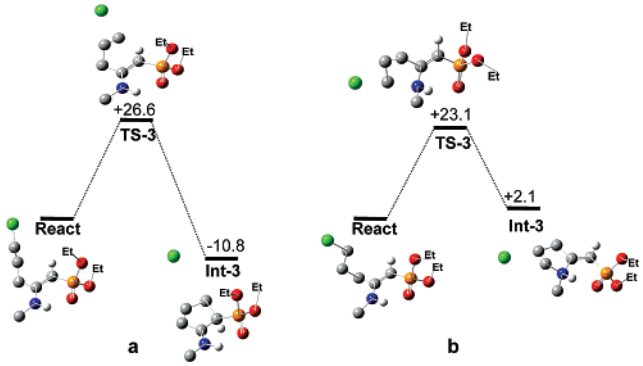


FIGURE 2. Calculated energy profile of: (a) C-cyclization and (b) N-cyclization of enamine. Energies (in kcal/mol) are obtained at the B3LYP/6-31G* level of calculation with PCM. Only nitrogen's hydrogens are depicted.

Furthermore, cyclization is best achieved by starting from the *Z* intermediate, where the lone pair is properly positioned to establish overlap with the C−Cl bond orbitals. Thus, calculations of the second step involved only the *Z* zwitterion (Figure 1a). As can be seen, the barrier for the cyclization reaction is not high (amounting to around 19 kcal/mol) at the B3LYP/6-31G* level and is even lower with larger basis sets (Table 1S in the Supporting Information). This result agrees well with the experimental observations that the reaction is relatively fast and proceeds at ambient temperature.

Finally, our calculations so far did not preclude the possibility of enamine formation, especially in the case of protic solvents, since we did not demonstrate that the environment is indeed not chemically reactive. Our assumption is that involvement of an enamine would lead to N-alkylation as was earlier observed by Lhommet.[16] Therefore, we calculated the reaction barrier for both C- and N-cyclization of the enamine, Figure 2. Additional results at various calculation levels are given as Supporting Information (Table 2S). We found that in both cases (C- or N-cyclization) the overall barrier for cyclization is predicted to be higher when the reaction proceeds through enamine compared with cyclization that follows the zwitterionic intermediate, suggesting that the latter would be the preferred mechanism. Moreover, the reaction barrier is found to be slightly lower for N-alkylation when compared to C-cyclization. This in turn

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(17) In the special case of a protic environment such as methylamine in water or ethanolamine, it is expected that protonation of the carbanion should be rapid. However, as indicated by calculations (unpublished) this step is reversible. Therefore, the direct cyclization of the carbanion, which leads to a very stable compound, serves as the driving force for the reaction and pushes the system toward its thermodynamically stable product.

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suggests that if enamine was an intermediate in the reaction, we would expect to obtain a mixture of both C- and N-cyclization with a ratio that favors the N-cyclization. This is obviously not the case, thus *leading us to conclude that the synthesis of the novel group of compounds* ***1*** *proceeds through a unique mechanism, involving the formation of a zwitterion followed by direct cyclization.*[19]

Experimental Section

General Procedure for the Synthesis of 1. To 0.238 g (1 mmol) of diethyl 5-chloro-1-pentynylphosphonate we added 2 mmol of the amine in a screw-capped 10 mL vial. After being stirred for 5 h at 25 °C, the reaction mixture was washed with aqueous 0.1 N $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 × 20 mL), separated on a silica gel column (10% methanol:90% dichloromethane), and analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

Competitive Reactions. To 1 mmol of diethyl 5-chloro-1-pentynylphosphonate and 1 mmol of diethyl 1-hexynylphosphonates we added 2 mmol of either benzylamine or isopropylamine in a screw-capped 10 mL vial. After the solution was stirred for 5 h at 25 °C the products were analyzed by ^{31}P NMR and GC/MS. Only compounds **1a** or **1h**, respectively, were detected. Similar results were obtained when the reactions were conducted in solution: 1 mL of THF or MeOH for 10 h at 25 °C.

$t_{1/2}$ Calculations. To 1 mmol of diethyl 5-chloro-1-pentynylphosphonate, or 1-hexynylphosphonate we added 2 mmol of benzylamine or ethanolamine in a screw-capped 10 mL vial at 25 °C. The reactions were followed by ^{31}P NMR and GC/MS. The $t_{1/2}$ values for formation of **1a** and **1h** were each estimated to be 1 h. The $t_{1/2}$ for the addition of either benzylamine or ethanolaminbe to diethyl 1-hexynylphosphonate was estimated to be 10 h.

Computational Details. All the calculations were performed with the Gaussian 03 program package.[20] Geometries were gradient-optimized and characterized by frequency analysis. Profiles were ascertained by following the reaction path, using the intrinsic reaction coordinate (IRC) technique with mass-weighted coordinates.[21] The effect of the solvent on the reaction profile was calculated with use of the PCM model.[22, 23]

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Supporting Information Available: Complete analytical data, scanned spectra of compounds **1a**−**k**, and stereochemical assignments; comparison of calculated energy profiles of the various reactions discussed using different levels; Cartesian coordinates, absolute energies, and number of imaginary frequencies of all calculated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Note that we did not investigate the corresponding 5-iodo and 5-bromo alkynylphosphonates since Ma has already demonstrated that 5-iodo-1-alkynylphosphonate reacts with amines to give azaheterocycles, presumably by an initial S_N2 attack on the C−I bond. In addition it is known that bromides are intermediate in their activity between iodides and chlorides. Thus, we believe that their investigation would not provide any additional insight to the mechanistic interpretation.

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